2017-00187 - Differential model reduction by \((\min,+)^\) tropical algebra constraint solving

**Level of qualifications required:** Graduate degree or equivalent

**Fonction:** PhD Position

### About the research centre or Inria department

Located at the heart of the main national research and higher education cluster, member of the Université Paris Saclay, a major actor in the French Investments for the Future Programme (Idex, LabEx, IRT, EquipeX) and partner of the main establishments present on the plateau, the centre is particularly active in three major areas: data and knowledge; safety, security and reliability; modelling, simulation and optimisation (with priority given to energy).

The 450 researchers and engineers from Inria and its partners who work in the research centre's 31 teams, the 100 research support staff members, the high-level equipment at their disposal (image walls, high-performance computing clusters, sensor networks), and the privileged relationships with prestigious industrial partners, all make Inria Saclay Île-de-France a key research centre in the local landscape and one that is oriented towards Europe and the world.

### Context

This thesis subject is offered at Inria Saclay Idf (https://www.inria.fr/en/centre/saclay) in the LIFEWARE project-team (http://lifeware.inria.fr), in the framework of the ANR-DFG SYMBIONT project on “Symbolic Methods for Biological Networks” (https://www.symbiont-project.org/).

The LIFEWARE team works in computational systems biology and develop the Biochemical Abstract Machine (BIOCHAM http://lifeware.inria.fr/biocham4) software for modeling, analyzing and now synthesizing biochemical reaction networks (CRNs) using methods from fundamental computer science and mathematics. The software developments are expected to be integrated in BIOCHAM.

The thesis will be supervised by François Fages who has supervised 29 Ph.D. theses in his career, the last defended in May 2016, and who currently is 100% available with no Ph.D. student.

### Assignment

Model reduction is a central topic in differential dynamical systems theory, for reducing the complexity of differential equations, finding important parameters, and developing multi-scale models for instance. While perturbation theory is a standard mathematical tool to analyze the different time scales of a dynamical system, and decompose the system according to fast-slow dynamics, in the domain of computational systems biology, the biochemical reaction networks under consideration involve several tenths of variables which appeal for automated reasoning methods.

Tropicalization is a mathematical method for analysing polynomial equations in the \((\min,+)^\) or \((\max,+)^\) semiring. The intuitive idea is to reason on the orders of magnitude of concentrations and kinetic parameters which are expressed by the logarithm of their values, hence the \((\min,+)^\) algebra for polynomials. We have shown that Constraint Logic Programming can be used to efficiently solve tropical equation problems for identifying the dominating monomials and reactions in a network, and then simplifying the dynamics in the different regions of the phase space corresponding to different regimes (i.e. Quasi Steady State or Quasi Equilibrium assumptions).

The goal of this Thesis, in collaboration with our partners of the ANR-DFG project SYMBIONT, is to generalize our tropical equation solver based on constraint programming to new stability constraints, and to develop the model reduction method by searching for precise approximation results (e.g. using Tikhonov theorem) at least in simple examples like the Michaelis-Menten enzymatic reaction. The method will be implemented in our modeling environment Biocham, evaluated on mcell systems biology models from BioModels repository, and compared to other symbolic methods developed in SYMBIONT.

### Main activities

Our first results on this subject have been published in


The planned work will consist in

- generalizing the CLP solver to handle inequalities instead of equalities, with accurate
translation from polynomials to (min,+) intervals,
- developing correctness criteria for the simplified system (e.g. stability conditions of Tikhonov theorem)
- implementing the model reduction method and evaluating it on models from the BioModels repository.

Further reading:

Skills
This subject requires common and basic knowledge on differential equations, linear algebra, algorithms and programming.

There is no specific prerequisite for this internship. However, some specific knowledge on either the algebra (max, +), constraint programming, control theory, or computational systems biology will be a plus.

Benefits package
- Subsidised catering service
- Partially-reimbursed public transport
- Social security
- Paid leave
- Flexible working hours
- Sports facilities

Remuneration
Monthly gross salary: 1.982 euros (1st and 2nd year) - 2.085 euros (3rd year)